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(Previously 910/21)

I am presently employed as researcher in the Hadassah-Hebrew University Hospital (Department of Oncology, Jerusalem 91120, Israel). I chair the Tumor Biology Research Unit of the Sharett Oncology Institute of the Hadassah Hospital. I am a full professor in the Faculty of Medicine of the Hebrew University School of Medicine. I received my Ph.D degree from the Weizmann Institute of Science (Rehovot, Israel) in 1975, worked as a post-doctoral fellow in the USA and UCSF and was a visiting Professor at Harvard Medical School (Children's Hospital, Boston). In 1980 I established a Tumor Biology Research Laboratory at the Hadassah-University Hospital. My research focuses on basic and clinical aspects of tumor metastasis and angiogenesis, with emphasis on cell adhesion with the extracellular matrix, heparin-binding growth factors and heparin/heparan sulfate-degrading enzymes. Since the beginning of my career, I have published 247 scientific articles in highly regarded journals and books, and

have presented my achievements at more than 90 international scientific conferences. I am a member of several international scientific societies and important local committees, and was awarded the 1997 prize for a distinguished Israeli scientist in medicine. For the last 20 years I have been engaged in the research of heparanase and heparan sulfate and have published over 70 papers in the field (see enclosed curriculum vitae). I am the head and scientific director of the group that was the first to report the cloning and recombinant expression of the heparanase gene.

I am a co-inventor of the subject matter claimed in the above-referenced U.S. patent application.

I have read the Examiner's Office Action dated November 7, 2000. I hereby declare the following:

Heparanase has a specific, well characterized and unique catalytic activity known for over 20 years. Over the years, heparanase was partially purified from a variety of mammalian sources. Heparanase is defined as a GAG hydrolase which cleaves heparin and heparan sulfate (both are sulfated) at the β 1,4 linkage between glucuronic acid and glucosamin. Heparanase is an endolytic enzyme and the average product length it generates is 8-12 saccharides. The other known heparin/heparan sulfate degrading enzymes are β -glucuronidase, α -L iduronidase and α -N acetylglucosaminidase. These three enzymes are exolytic enzymes, each of which cleaves a specific linkage within the polysaccharide chain and generates disaccharides. These issues are further addressed below.

There are three sources of reports regarding false heparanase antibodies as follows:

An anti PAI-1 antibody, which is described in U.S. Pat. No. 5,362,641, was produced in an attempt to elicit anti-heparanase antibodies. This antibody was

elicited by a PAI-1 contamination in a purified sample of heparanase, as was observed by peptide analysis.

Identification of this antibody as an anti PAI-1 antibody is discussed in U.S. Patent No. 5,968,822 (Application No. 08/922,170, from which priority is claimed. Page 11, line 18 to page 12, line 2, recite in this respect that:

Several years ago we prepared rabbit polyclonal antibodies directed against our partially purified preparation of human placenta heparanase. These antibodies, referred to in U.S. Pat. No. 5,362,641, were later found to be directed against plasminogen activator inhibitor type I (PAI-1) that was co-purified with the placental heparanase. These findings led to a modification of the original purification protocol to remove the PAI-1 contaminant.

Another false anti-heparanase antibody was generated against the chemokine CTAP III, a protein that was reported to possess heparanase-like activity. These antibodies were generated by the group of Prof. Ledbetter as described in Hoogewerf et al. J Biol Chem 17;270(7):3268-77, 1995) and were donated to other researchers as reported by Kosir et al. (J Surg Res. 67(1):98-105, 1997, page 99, materials and methods, right column, western blot).

CTAP III is a low molecular weight chemokine, which has no homology to heparanase from human placenta, SK-hepatoma, platelets (Hullet et. al. Nat. Med 5(7): 803-809, 1999) and SV40 transformed fibroblasts (Toyoshima and Nakajima J. Biol. Chem. 274(34):24153-24160, 1999) which were all purified and cloned recently and correspond to the amino acid sequence set forth in SEQ ID NO. 2 of U.S. Patent No. 5,968,822 (Application No. 08/922,170).

Because CTAPIII and heparanase, as defined by SEQ ID NO:2 of U.S. Patent No. 5,968,822 (Application No. 08/922,170), share no sequence homology, these antibodies are irrelevant. In addition, it was declared and it is now accepted

by the scientific community, as is recited below, that CTAPIII was erroneously thought to be heparanase.

The third false anti-heparanase antibody was generated in the laboratory of Prof. Nicolson and was first reported by Jin et al. (*Int J Cancer*. 45(6):1088-95, 1990). This group isolated a 96 kDa mouse protein and used a peptide derived from the N-terminus of the partially purified protein to generate polyclonal as well as monoclonal antibodies. These antibodies detect a 96 kDa protein, which is obviously different from the placental heparanase referred to in the instant application and which was later isolated from other tissues as currently reported by several other groups. These antibodies were used by several research groups in collaboration with either one of the authors of the original paper (Marchetti et al. *Cancer Res*. 56(12):2856-63, 1996, Marchetti and Nicolson, *Adv Enzyme Regul*. 37:111-34, 1997, Mollinedo et al. *Biochem J*. 327(3):917-23, 1997). In 1994, Vouge et al. (*Int. J. Cancer* 56:286-294, 1994) pointed out the fact that the antibodies claimed to detect heparanase actually detect GR94/endoplasmic reticulum protein, a previously cloned and characterized murine heat shock protein. The sequence and the molecular weight were in perfect agreement with those reported for the 96 kDa murine heparanase isolated by Nicolson's group. Later on, the mis-identification of the heparanase enzyme and consequently the antibodies generated against it was admitted and accepted by the scientific community. The late papers (1996, 1997) still referring to these antibodies, as heparanase specific, are obscure. There is no doubt, however, that those antibodies do not recognize heparanase. Interestingly, Prof. Nicolson has abandoned heparanase research and does not take part in the major progress achieved during the recent years. Dr. Nakajima is a researcher at Novartis, a company that published recently the cloning of heparanase, with Nakajima as a last author (Toyoshima and Nakajima, *J. Biol. Chem*. 274(34):24153-24160, 1999). The published sequence is identical to SEQ ID

NO:2 of U.S. Patent No. 5,968,822 (Application No. 08/922,170) and the molecular weight of the purified protein is of 50 kDa.

These falls anti-heparanase antibodies are further addressed below.

The following provides a more detailed insight relating to the catalytic activity of heparanase, which activity is known for over 20 years and is unique over all other heparin or heparan sulfate degrading enzymes.

The enzymatic degradation of glycosaminoglycans is reviewed By Ernst et al. (Critical Reviews in Biochemistry and Molecular Biology , 30(5):387-444 (1995)). Ernst et al. describe the structure of various GAGs, the enzymatic degradation process thereof and the enzymes involved in such degradation. The common feature of GAGs structure is repeated disaccharide units consisting of a uronic acid and hexosamine. Various GAGs differ in the composition of the dunits and in type and level of modifications, such as C5-epimerization and N or O-sulfation. Sulfated GAGs include heparin, heparan sulfate chondroitin sulfate, dermatan sulfate and keratan sulfate. Heparan sulfate and heparin are composed of repeated units of glucosamine and glucuronic/iduronic acid, which undergo modifications such as C5-epimerization, N-sulfation and O-sulfation. Heparin is characterized by a higher level of modifications than heparan sulfate.

GAGs can be depolymerized enzymatically either by eliminative cleavage with lyases (EC 4.2.2.-) or by hydrolytic cleavage with hydrolases (EC 3.2.1.-). Often, these enzymes are specific for residues in the polysaccharide chain with certain modifications. GAG degrading lyases are mainly of bacterial origin. In the eliminative cleavage, C5 hydrogen of uronic acid is abstracted, forming an unsaturated C4-5 bond, whereas in the hydrolytic mechanism a proton is donated to the glycosidic oxygen and creating an O5 oxonium ion followed by water addition which neutralizes the oxonium ion and saturates all carbons (Lindhart et al. 1986, Appl. Biochem. Biotech. 12:135-75). The lyases

can only cleave linkages on the non-reducing side of the of uronic acids, as the carboxylic group of uronic acid participates in the reaction. The hydrolyses, on the other hand, can be specific for either of the two bonds in the repeating disaccharides.

In pages 414 and 424 of the review, tables 8 and 14, Ernst et al. list the known GAG degrading enzymes. These tables describe substrate specificity, cleavage mechanism, cleavage linkage, product length and mode of action (endo/exolytic). Heparanase is defined as a GAG hydrolase which cleaves heparin and heparan sulfate at the β 1,4 linkage between glucuronic acid and glucosamin. Heparanase is an endolytic enzyme and the average product length is 8-12 saccharides.

The other known heparin/heparan sulfate degrading enzymes are β -glucuronidase, α -L iduronidase and α -N acetylglucosaminidase which are exolytic enzymes, each one which cleaves a specific linkage within the polysaccharide chain and generates disaccharides.

In table 8 the authors list two heparanases; platelet heparanase and tumor heparanase, which share the same substrate and mechanism of action. These two were later on found to be identical at the molecular level as well (Freeman et al. *Biochem J.* (1999) 342, 361-268, Vlodavsky et al. *Nat. Med.* 5(7):793-802, 1999, Hullet et al. *Nature Medicine* 5(7):803-809, 1999).

Thus, heparanase, which is known for over 20 years, has a unique and well characterized endolytic activity, endo- β -D-glucouronidase, towards heparin and heparan sulfate.

The phrase heparanase (endo- β -D-glucouronidase) protein" and hence monoclonal antibodies recognizing same relate to a specific and well defined group of species.

I turn now to a detailed discussion of the references cited by the Examiner in the recent Official action and which are said to teach anti-heparanase antibodies.

U.S. Pat. No. 5,332,812 describes the use of a solid phase substrate for determination of heparanase activity. An alternative approach for immuno-quantitation of heparanase is proposed, using heparanase specific antibodies. Column 11, lines 22-44 of U.S. Pat. No. 5,332,812 recite:

The assay measuring levels of a glycosaminoglycan endoglycosidase such as heparan sulfate endoglycosidase (heparanase) may also be performed in an immunoassay format using polyclonal and/or monoclonal antibodies raised to the endoglycosidase. Preferably, antibodies with relatively low cross-reactivity to other endoglycosidases, such as the platelet endoglycosidase described by Oldberg, et al. (1980) Biochem., V 19, pp 5755-5762, can be used. The antibodies may be used with a variety of immunoassay techniques to measure the endoglycosidase protein directly. The endoglycosidase may be measured by either a radioimmunoassay described by Berson and Yalow (1968) Clin. Chem, Acta., V 22, p 51 or an immunoradiometric (IRMA) assay described by Miles, et al. (1976) Anal. Biochem., V 61, pp 209-224 using ¹²⁵I-labeled antigen or antibody. The endoglycosidase may also be measured by an enzyme immunoassay that uses either a competitive-binding assay or a "sandwich" assay analogous to an IRMA and using alkaline phosphatase, horse radish peroxidase, or any other enzyme coupled to an antibody or to the endoglycosidase as reviewed by Wisdom (1976) Clin. Chem., V 22, pp 1243-1255. (emphasis added)

The concept of immunoassay of proteins using specific antibodies recognizing same is well known in the art for a long time. However, no example of an anti-heparanase antibody is disclosed in U.S. Pat. No. 5,332,812. The authors define the preferable antibody as non cross-reactive with the platelet

endoglycosidase described by Oldberg et al. (Biochem. 19:5755-5762, 1980). Oldberg et al. fail to describe or use in their paper any heparanase antibodies. Thus, the source for anti-heparanase antibodies remains obscure.

As is evident from the background section of the instant application, the response filed herewith (see in particular the concluding remarks, and the arguments) and this declaration, the need for anti-heparanase antibodies is well recognized for many years and many unsuccessful attempts were made to obtain such antibodies. U.S. Pat. No. 5,332,812 clearly recognizes a particular need for anti-heparanase antibodies, however, recognizing a need does not qualify as anticipation. The need for anti-heparanase antibodies is indeed recognized by the art. However, this need was not fulfilled by the prior art, nor does U.S. Pat. No. 5,332,812 fulfill this need.

Thus, U.S. Pat. No. 5,332,812 fails to teach anti-heparanase antibodies.

Marchetti et al. briefly mention the use of antibody developed against heparanase. No description of an antibody source, preparation or characteristics is provided. No data is shown regarding such an antibody. The authors refer to a manuscript in preparation. I failed to find any later publications which provide this data. In a similar paper published by Marchetti and Nicolson (Adv Enzyme Regul. 37:111-34, 1997) the same "results" are briefly described with the remark "data not shown" (see, page 127, the paragraph just before the discussion). In a more recent paper which discusses heparanase regulation in human melanoma and where Marchetti is the last author, the results are based solely on activity measurements (Walch et al. Int. J. Cancer 82:112-120, 1999). Mollinedo et al. (Biochem J. 327(3):917-23, 1997) report localization of heparanase using the monoclonal antibody and refer on page 918 (materials and methods, antibodies) to Marchetti et al. (Cancer Res. 56:2856-2863, 1996). Mollinedo et al. show immunoblots where the heparanase antibody detects a 96 kDa protein (page 920, Figure 2).

It is my knowledge that this antibody was generated in the laboratory of Prof. Nicolson and was first reported by Jin et al. (Int J Cancer. 45(6):1088-95, 1990). This group isolated a 96 kDa mouse protein and used a peptide derived from the N-terminus of the partially purified protein to generate polyclonal as well as monoclonal antibodies. These antibodies detect a 96 kDa protein, which is obviously different from placental heparanase and which was later isolated from other tissues as currently reported by several groups. These antibodies were used by several research groups in collaboration with either one of the authors of the original paper (Marchetti et al. Cancer Res. 56(12):2856-63, 1996, Marchetti and Nicolson, Adv Enzyme Regul. 37:111-34, 1997, Mollinedo et al. Biochem J. 327(3):917-23, 1997). In 1994, Vouge et al. (Int. J. Cancer 56:286-294, 1994) pointed out the fact that the antibodies claimed to detect heparanase actually detect GR94/endoplasmic reticulum protein, a previously cloned and characterized murine heat shock protein. The sequence and the molecular weight were in perfect agreement with those reported for the 96 kDa murine heparanase isolated by Nicolson's group. Later on, the mis-identification of the heparanase enzyme and consequently the antibodies generated against it was admitted and accepted by the scientific community (see attached declaration). The late papers (1996, 1997) still referring to these antibodies, as heparanase specific, are obscure. There is no doubt in my mind and it is well accepted by the scientific community that those antibodies do not recognize heparanase. Interestingly, Prof. Nicolson has abandoned heparanase research and does not take part in the major progress achieved during the recent years. Dr. Nakajima is a researcher at Novartis, a company that published recently the cloning of heparanase, with Nakajima as a last author (Toyoshima and Nakajima, J. Biol. Chem. 274(34):24153-24160, 1999). The published sequence is identical to SEQ ID NO:2 listed in U.S. Patent No. 5,968,822 (Application No. 08/922,170) and the molecular weight of the purified protein is of 50 kDa.

Heparanase is a very attractive enzyme. Besides the scientific interest its biological function suggests a clear pharmaceutical potential. Several research groups as well as biotechnology companies invested immense effort in purification and in cloning attempts. Following the first clues, four groups have cloned and published the heparanase sequence, all by means of activity assays, including, as already noted, Nakajima which was among the generators of the antibodies raised against the 96 kDa murine protein. It is very unlikely that a group having heparanase specific antibodies will not take advantage of such a powerful tool in cloning the heparanase gene. The recently published four independent reports define heparanase unequivocally and with a perfect consensus as a 50 kDa protein in human as well as in mouse and rat (Freeman et al. *Biochem J.* 342(2):361-368, 1999). This enzyme is clearly unrelated to the 97 kDa murine protein.

Kosir et al. provided yet another source of confusion in the field of heparanase, which confusion has now been resolved. Kosir et al. disclose anti-CTAP III antibodies, CTAP III is a platelet derived chemokine to which heparanase activity was erroneously attributed in the past. No sequence homology is observed between CTAP III and heparanases derived from, for example, placenta and from hepatoma cells (SEQ ID NO:2 of U.S. Patent No. 5,968,822 (Application No. 08/922,170), Vlodavsky et al. *Nat. Med.* 5(7):793-802, 1999, Kosir et al. *Biochem Biophys Res Commun.* 261(1):183-7, 1999) and as was later reported, from platelets (Hullet et al. *Nature Medicine* 5(7):803-809, 1999) and from SV40 transformed fibroblasts (Toyoshima and Nakajima *J. Biol. Chem.* 274(34):24153-24160, 1999).

The antibody used by Kosir et al. (*J Surg Res.* 67(1):98-105, 1997) was donated thereto by Dr. Ledbetter. According to lines 15-16 of the "Western blot" section, production of these antibodies was described in Hoogewerf et al. (*J. Biol.*

Chem. 270(7): 3268-77, 1995). In this paper Hoogwerf et al., a research group from Upjohn Company, Kalamazoo, Michigan, describe the identification of CXC chemokines (the CTAPIII family) as heparan sulfate degrading enzymes. The antibodies described in the paper were raised against CTAPIII, which shares no sequence homology with the 50 kDa heparanase. Moreover, in a recent paper the same group from Pharmacia and Upjohn, Inc. retracted from their earlier statement regarding the heparanase activity of CTAPIII (Fairbank et al. J Biol Chem 274(42): 29587-29590, 1999) page 29590, right column, last paragraph of the discussion. They state that:

Finally, an earlier report from this laboratory suggested that heparanase was a post-translationally modified form of a CXC chemokine, namely CTAPIII (7). We have not been able to confirm this observation, nor have others who have purified and characterized human heparanase

In this paragraph they refer to their previous paper, Hoogwerf et al. (J Biol Chem 1995 Feb 17;270(7):3268-77) as discussed above.

It is accepted today by the scientific community that CTAPIII is not a heparanase or a precursor thereof.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

January 6, 2001


Prof. Israel Vlodavsky

CURRICULUM VITAE

Name: Israel Vlodavsky
 Date & Place of Birth: August 31, 1944, Israel
 Nationality: Israeli
 Martial Status: Married, three children
 Military Service: Israel Defence Forces (1963-65)

Education:

1968 B.Sc. Biochemistry and Microbiology, Hebrew University of Jerusalem.

 1970 M.Sc. Department of Biochemistry, Hebrew University of Jerusalem. Thesis: "Properties of Calcium Binding and Active Transport in Sarcoplasmic Reticulum" under the supervision of Prof. Zvi Selinger.

 1975 Ph.D. Weizmann Institute of Science, Rehovot, Israel. Thesis: "Lectins as Probe for Changes in Membrane Dynamics in Malignant Cell Transformation" under the supervision of Prof. Leo Sachs.

 1976-1977 Postdoctoral Research under the supervision of Prof. C.F. Fox, Molecular Biology Institute, University of California, Los Angeles.

 1977-1978 Postdoctoral Research under the supervision of Prof. D. Gospodarowicz, Cancer Research Institute, University of California, San Francisco.

Professional Experience:

1978-1979 Associate Research Biochemist, Cancer Research Institute, University of California, San Francisco.

 1979-1981 Lecturer, Dept. of Radiation & Clinical Oncology Hadassah University Hospital, Jerusalem, Israel.

 1981-1984 Senior Lecturer in Experimental Oncology, Dept. of Oncology, The Hebrew University-Hadassah Medical School.

 1984-1990 Associate Professor in Experimental Oncology, Dept. of Oncology, The Hebrew University-Hadassah Medical School.

 1985-1986 Visiting Professor, Dept. Surgical Research, Harvard Medical School, Boston.

 1990-present Professor, Dept. of Oncology, Hadassah-Hebrew University.

Current Position: Head, Tumor Biology Research Unit, Hadassah-Hebrew University Hospital.

1997 Elkeles prize - 1997 Distinguished scientist in Medicine

Ph.D. Students: Bar-Ner, M; Fridman, R; Bashkin, P; Benezra, M; Levi, E; Miao Hau-Quan; Elkin, M., Even-Ram, S.

Zecharia, E., Goldshmidt, O., Yedovitzky, Y., Bitan, M., Kovalshuk, O.; Aviv, A.

Key words: Extracellular Matrix; Angiogenesis; Metastasis; Heparan sulfate; Heparanase; Heparin-binding growth factors, Tumor progression

Research Topics:

1. Mammalian heparanase: Involvement in tumor metastasis and angiogenesis.
2. Mammalian heparanase: Involvement in inflammation and autoimmunity.
3. Heparan sulfate proteoglycans, heparin-binding growth factors and heparin-mimicking compounds.
4. Control of cell proliferation and differentiation by the extracellular matrix.
5. Vascular endothelial and smooth muscle cells, neo-vascularization and restenosis.

Research Fellowships and grants:

1976	Research Training Fellowship, UICC
1976	U.S. Public Health Service; Fogarty International Center
1977	Chaim Weizmann Postdoctoral Fellowship, Feinberg Graduate School,
1980-1983	The Israel Academy of Sciences
1980-1982	The Israel Cancer Research Fund (ICRF)
1980-1982	Israel Cancer Association
1981-1984	U.S.A.-Israel Binational Science Foundation
1981-1984	National Cancer Institute, NIH (RO1-CA 30289)
1983-1985	NCRD-DKFZ Cooperation in Cancer Research
1984-1987	The Israel Academy of Sciences
1984-1989	Leukemia Society of America
1985-1988	National Cancer Institute, NIH (RO1-CA 30289)
1987-1990	Applied Research Supported by KabiVitrum AB, Stockholm
1987-1993	Applied Research Supported by ImClone Systems, New York
1987-1990	U.S.A. - Israel Binational Science Foundation
1988-1990	The Israel Cancer Research Fund (ICRF)
1988-1991	German-Israel Foundation for Scientific Research & Development (GIF)
1988-1992	Applied Research Supported by Rhone-Poulenc Rorer Co., Philadelphia
1989-1992	National Cancer Institute, NIH (RO1-CA 30289)
1992-1993	Ministry of Health.
1993-1994	The Israel Cancer Research Fund (ICRF)
1992-1995	U.S.A. - Israel Binational Science Foundation
1993-1996	The Israel Science Foundation
1993-1995	Applied Research Supported by IBEX Technologies, Montreal Quebec
1994-1998	The Israel Science Foundation (Excellence Research Center)
1995-1997	Ministry of Health
1995-1998	Joint German-Israeli Research Projects (MOSA-BMBF)
1996-1999	German-Israel Foundation for Scientific Research & Development (GIF)
1995-1997	Joint Japan-Israeli Research Projects
1996-2000	Applied Research Supported by Collgard/IPC, Medica Israel
1997-2000	Applied Research Supported by InSight pharmaceuticals Ltd., Israel
1998-2001	The Israel Science Foundation
1998-2001	Association for International Cancer Research, UK
1998-2000	Middle East Cancer Consortium (MECC)
1999-2002	NCRD-DKFZ Cooperation in Cancer Research
1999-2000	Center for the Study of Emerging Diseases
1999-2001	Hadasit-Applied Research
2000-2003	U.S Army Breast Cancer Program
2000-2002	NIH Breast Cancer Program

LIST OF PUBLICATIONS

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2. Vlodavsky, I., Inbar, M. and Sachs, L. Temperature sensitive agglutinability of human erythrocytes by lectins. *Biochim. Biophys. Acta* 274:364-368, 1972.
3. Inbar, M., Vlodavsky, I. and Sachs, L. Availability of L-Fucose-like sites on the surface membrane of normal and transformed mammalian cells. *Biochim. Biophys. Acta* 205:703-705, 1972.
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11. Vlodavsky, I. and Sachs, L. Difference in the calcium regulation of concanavalin A agglutinability and surface microvilli in normal and transformed cells: Relationship to membrane-cytoskeleton interaction. *Exptl. Cell Res.* 105:179-189, 1977.
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Book Chapters and Review Articles

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3. Gospodarowicz, D., Vlodavsky, I., Greenburg, G. and Johnson, L.K. Cellular shape is determined by the extracellular matrix and is responsible for the control of cellular growth and function. In: Hormones and Cell Culture (R. Ross and G. Sato, eds.) Cold Spring Harbor Conference on Cell Proliferation, V.6, Cold Spring Harbor, NY, 561-592, 1979.
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63. Israel-France symposium on extracellular matrix (Jerusalem, April 1995)
64. Tumor microenvironment (Tiberias, May 1995)
65. XVth Int. Congress on Thrombosis & Haemostasis (Jerusalem, June 1995)
66. 6th Conference on Differentiation Therapy (Herzlia, June 1995)
67. The annual meeting of EVBA (Goteborg, Sweden, June 1996)
68. IX International Vascular Biology Meeting (Seattle, Washington, September 1996)
69. 4th Annual Scandinavian Atherosclerosis Conference (Copenhagen, May 1997)
70. 7th International Symposium on Cardiovascular Pharmacotherapy (Jerusalem 1997)
71. Denmark Symposium: Chronic Diseases Processes (Copenhagen, September 1997)
72. International Cancer Microenvironment Forum (London, October 1997)
73. Gordon Conference on proteoglycans (New Hampshire, July 1998)
74. Xth International Vascular Biology Meeting (Cairns, Australia, August 1998)
75. 70th European Atherosclerosis Society congress (Geneva, September, 1998)
76. F.I.S.E.B. (Israeli Societies of Experimental Biology-Eilat, December, 1998)
77. 1st Anglo-Israel Cancer Conference (Eilat, December, 1998).
78. Forbeck Focus Seminar on Tumor Metastasis (Ein-Cedi, February, 1999)
79. Wenner-Gren International Symposium (Stockholm, April, 1999)
80. The International Cancer Microenvironment Forum (Pittsburgh, October, 1999)
81. Vasculogenesis and Angiogenesis (Capri, October, 1999)
82. Bat-Sheva Seminar on Cell Adhesion (Dead Sea, November, 1999)
83. 91st. AACR annual meeting (San-Francisco, April, 2000)
84. Hinterzartener Kreis Cancer Progression meeting (Lake Como, Italy)
84. VIIIth Int. Congress, Metastasis Research Society (London, Sep. 2000)
85. 2nd. Int. Conference on Tumor Microenvironment (Tiberias, October, 2000)
86. AACR Conference on New Targets for Cancer Intervention (Eilat, Nov. 2000)

Teaching (courses taught)

- Biology of the cell (# 94625; structural and functional aspects; 1st year medical students).
- Growth factors and cytokines (# 81891, signaling and clinical applications).
- Selected topics in cancer research (# 94807; angiogenesis, metastasis).
- Cell-cell & Cell-matrix interactions (# 94843; Integrins, cell adhesion molecules, heparan sulfate proteoglycans and other components of the ECM).
- Other topics: Vascular Biology (vessel wall, restenosis, atherosclerosis).

University/Hospital activities

- | | |
|---------------|---|
| 1986-1989 | Head, Cell Biology Committee - Authority for Ph.D Research Students, The Hebrew University of Jerusalem. |
| 1986-1990 | Research Committee (Hadassah University Hospital). |
| 1990-present | Board of Directors (Hadasit-Medical Research Services & Development Ltd.). |
| 1991-present | Applied Research Committee (Hadassah University Hospital). |
| 1995-present— | Promotion Committee (Morphological & Biomedical Sciences; Faculty of Medicine, Hebrew University of Jerusalem). |
| 1996-1999 | Top Committee for Appointments & Promotions (Faculty of Medicine, Hebrew |
| 1997-present | Steering Committee - Goldyne Savad Institute of Gene Therapy (Hadassah Medical Organization). |

National & activities

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| 1995 - 1998 | Research grants Committee - Ministry of Health. |
| 2000 - present | Head, Research grants Committee (Cell Biology) - The Israel Science Foundation. |
| 2000 - present | Alon Committee - Council for Higher Education. |
| 2000 - present | Science Vision Committee - Minister of Science, Culture & Education. |